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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,962	11/08/2000	Bernhard Hauer	49041	7018

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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,962	HAUER ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 5-9 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 5-9, as amended and newly added, are rejected under 35 U.S.C. 103(a) as being unpatentable over Volz et al (Journal of Chromatography) in view of Guerinot et al (5,846,821) and Haymore et al (EP 409,814) for reasons of given below.

Volz et al discloses at page 32, col. 2, a peptide fragment of ATPase (1-51) of formula HxHxxxCxxC. A species of this generic peptide fragment is disclosed at page 34, Fig. 2, compound (a), ATPase-439 (1-51). Volz further discloses at page 29, col. 1 that a number of peptides and proteins containing certain motifs of histidine and cysteine residues are known to specifically bind divalent transition metal ions. Typical binding sites for Cu+2, Zn+2 and Ni+2 ions comprise CxxC motifs. Volz also discloses that that the metal binding property of the peptide fragment reside in the presence of the two His and Cys residues. Guerinot discloses at col. 14, line 27 that conservative amino acid residues e.g., Leu and Ile can be

substituted with one another, especially in the non-essential positions. Ile is a known homolog of Leu. Haymore, like Guerinot, discloses at page 4, line 12 peptide fragments that are metal binding peptides where the nature of the intervening residues is relatively unimportant. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to pick and choose from the 20 naturally occurring amino acid, the ones that can occupy the x positions in the peptide sequence motif of Volz. Haymore, Guerinot and Volz all disclose that amino acids at the non-critical or intervening residues between the His and Cys metal binding residues are relatively unimportant in the binding of peptide fragments to metals. One would reasonably expect successful binding of the peptide fragments to metal ions since all of the prior art teaches the binding resides in the critical motif of His and Cys residues.

The Board pointed out that in the Answer (page 9), the examiner argues that "Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues." In this regard, we find that Volz refers to the different metal ion binding regions as "motifs." For example, Volz describes the correspondent peptide as containing a

H-X-H-X-X-X-C-X-X-C motif. See, e.g., the abstract. Thus, Volz suggests, and Haymore confirms (p. 4, lines 10-13), that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. In addition, Haymore states that the intervening residues are not important. Accordingly, the teachings of Volz and Haymore would have suggested that any naturally-occurring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif. This would include the amino acids recited in claims 5 and 6.

Response to Arguments

Applicants argue that none of the pending claims recite peptides containing Ile in the X3 position, meaning that the prior art does not contain the elements of the claimed invention.

In response, although none of the claims recite Ile, it does not obviate the finding of obviousness that any of the 19 amino acid residues, besides Ile can occupy the x positions, as taught by the references.

Applicants assert that the residues specified in the claims create sequences of unique importance far from the teachings of the prior art, and there is support for this fact in the specification. The specification states at page 4, lines

19-26, that "it is advantageous for at least one of the variables X1 to X6 in the sequence additionally to be, independently of one another, Lys or Arg. Further advantageous amino acids present in the variables X1 to X6 are Glu, Lys, Arg, Tyr, Cys, Lys, His, Asp or Met. The amino acids Cys, Glu, Lys, Tyr or Arg are preferably present, particularly- preferably Cys. These amino acids contribute to the advantageous binding of the peptide fragments to the immobilized metal ions." These advantages are the reason for the importance of the specific substituents disclosed in previous claim 5.

In reply, that unique sequences would be obtained if any of the 20 naturally occurring amino acids can occupy any of the intervening residues is expected. To determine which sequences are better binders would be within the ordinary skill in the art as taught by Volz.

Volz discloses at page 37, col. 1, paragraph 5:

> ESI-MS and metal chelate affinity chromatography revealed different metal ion selectivity of these peptide sequences. As general motifs for Ni+2 ion binding, sequences were identified which contain two or more histidine residues in close proximity i.e. HxH and HxxH. Cysteine-containing motifs such as CxxC were capable to bind Cu+2 but not Ni+2 ions. Ni-NTA chromatography was used to effectively purify ATPase-439, and Cu-NTA chromatography to separate APP from non-metal-binding proteins. Since the isolation of the native APP-protein has been found difficult so far, the observed metal ion specificity may lead to an improved purification procedure. Furthermore, the

> present study demonstrates the possibility of protein purification from metal chelate chromatography without using an additional oligo- histidine (His-tag) sequence, ***indicating the efficient NTA chromatographic purification of proteins having suitable natural binding motifs.*** (Emphasis supplied).

The findings of Volz that some sequences preferentially bind one metal from the other are confirmed by applicants' subsequent arguments in the instant REMARKS:

> The variables claimed in SEQ ID NO:2 through SEQ ID NO:5 of claims 6-9 are a particularly preferred peptide fragment. See page 5, lines 23-31. Primary support for the importance of SEQ ID NO: 2 through 5 can be found in Example 6 of the specifications (page 19), which illustrates some of the experiments performed by the inventors. In these experiments, claimed SEQ ID NOs. 2, 3, 4 and 5 bind well to the nickel metal chelate column, whereas other tested variations on the HxHxxxCxxC formula, show no binding. Specifically, SEQ ID NO:3 produced a protein yield of 56%, which is higher than the 48% with the his tags. SEQ ID NO:3 also showed preferred binding to Ni2+ and Cu2+, while no binding to Zn2+ was observed. "On use of Ni chelate columns, the clone M13 [corresponding to SEQ ID NO:3] showed distinctly better purification of the proteins by comparison with the his tags. Conversely, the latter resulted in a purer product by comparison with M13 on use of Cu chelate columns." (Specification page 20, lines 29-35.)

Accordingly, as stated by the Board above, the teachings of Volz and Haymore would have suggested that any naturally-occurring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif. This would include the amino acids recited in claims 5 and 6.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is (571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0765. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

T. D. Wessendorf
Primary Examiner
Art Unit 1639

Tdw
February 7, 2007